The opinion in support of the decision being entered today is not binding precedent of the Board.

Paper 46

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

WEI-WEI ZHANG
and
JACK ROTH

Junior party,
Application 08/222,285

v.

JEAN-LUC IMLER, MAJID MEHTALI
and ANDREA PAVIRANI

Senior party,
Application 09/218,143

Patent Interference No. 104,823 (CAS)

Before: TORCZON, SPIEGEL and TIERNEY, Administrative Patent Judges.

SPIEGEL, Administrative Patent Judge.

MEMORANDUM OPINION and FINAL JUDGMENT
(Decision on preliminary motions)

I. Introduction

Imler preliminary motion 1 was withdrawn in favor of the motion resubmitted as

Imler preliminary motion 2 (Paper 39).[1] Imler preliminary motion 2 moves pursuant to 37 CFR § 1.633(b) for judgment that there is no interference-in-fact between the involved claims of Imler application 09/218,143 (Imler '143) and the involved claims of Zhang application 08/222,285 (Zhang '285) (Paper 40). Zhang opposes (Paper 41); Imler replies (Paper 44).

Imler argues that "Zhang's claims designated to correspond to the count require all of the E2 region to be deleted whereas none of Imler's claims require all of the E2 region to be deleted" (Paper 40, pp. 1-2). Zhang argues that "[e]ach of Party Imler's [corresponding] claims ... encompass a recombinant adenovirus which has all or part of the E2A region removed. In contrast, each of Party Zhang' [corresponding] claims ... encompass adenoviral vectors constructs in which the entire E2 coding region is removed" (Paper 43, p. 5). Zhang further argues that "there is no interference-in-fact based on the 'E2A deletion' *versus* 'all of E2 deletion' distinction" (Paper 41, p. 3).

Zhang contemporaneously filed Zhang preliminary motion 1 (to substitute an application, Zhang 10/246,696 (Zhang '696) (Ex 2001) with new claims 28-48 encompassing adenoviral vector constructs having all or a part of the E2 coding region deleted), arguing that the subject matter of Zhang '696 claims 28-48 interfere with the subject matter of Imler '143 claims 56, 57, 59 and 61-65 (Paper 42). Zhang additionally filed Zhang preliminary motion 2, proposing to substitute the existing count with "substitute count 1" and to designate Zhang '696 claims 28-48 and Imler '143 claims 56, 57, 59 and 61-65 as corresponding to "substitute count 1" (Paper 43, pp. 6-7).

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[1] Also see Paper 38, "ORDER AUTHORIZING RESUBMISSION OF RULE 633(b) MOTION."

Imler urges us "to issue judgment that there is not an interference-in-fact between the existing claims of the parties, and to dismiss Zhang Preliminary Motions 1 and 2" (Imler Reply 2, Paper 44).

We grant Imler preliminary motion 2 and enter a recommendation that Imler '143 claims are unpatentable under 35 U.S.C. § 112, first paragraph (lack of adequate written description and lack of enablement) because the "comprising" language of Imler's involved claims encompasses recombinant adenoviruses additionally having all of the E2B (i.e., all of the E2) region removed. We further dismiss Zhang preliminary motions 1 and 2, without prejudice to further proceedings before the primary Examiner.

II. Findings of fact

The following facts are supported by a preponderance of the evidence.

Junior party

F1. The junior party is Wei-Wei Zhang and Jack Roth (**Zhang**).

F2. Zhang is involved in the interference on the basis of U.S. application 08/222,285, filed April 4, 1994.

F3. The real party in interest is BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM.

Senior party

F4. The senior party is Jean-Luc Imler, Majid Mehtali and Andrea Pavirani (**Imler**).

F5. Imler is involved in the interference on the basis of U.S. application 09/218,143, filed December 22, 1998.

F6. Imler '143 has been accorded benefit for the purpose of priority of

U.S. application 08/379,452, filed January 26, 1995,
PCT application PCT/FR94/00624, filed May 27, 1994, and
FR application 93 06482, filed May 28, 1993.

F7. The real party in interest is TRANSGENE S.A.

The interference

F8. The subject matter of the interference is defined by one Count.

F9. Count 1 (Paper 1, p. 5) reads:

Count 1

The adenovirus construct of claim 28 of the '285 Zhang application

or

The recombinant adenovirus of claim 56 of the '143 Imler application

or

The recombinant adenoviral vector of claim 62 of the '143 Imler application.

F10. Zhang '285 claim 28 reads:

The adenovirus vector construct of claim 1, wherein only the E2 region is deleted.

F11. Zhang '285 claim 1 reads:

An adenovirus vector construct, wherein all of the E2 coding region has been deleted from the adenovirus genome and heterologous DNA is inserted in its place, but specifically excluding an adenovirus vector from which each of the E1, E2, E3 and E4 coding regions have been deleted.

F12. Imler '143 claim 56 reads:

A recombinant adenovirus comprising an adenovirus genome having a foreign gene and a promoter for expressing said foreign gene, wherein the function of an E2A gene is completely deleted by removing a part or all of said E2A gene.

F13. Imler '143 claim 62 reads:

> A recombinant adenoviral vector comprising an adenovirus genome having a foreign gene and a promoter for expressing said foreign gene, wherein the function of an E2A adenoviral gene is completely deleted by removing a part or all of said E2A gene.

F14. The claims of the parties are:

Zhang '285:	1-10, 15-23, 28-51[2]
Imler '143:	56-57, 59, 61-65

F15. The claims of the parties which correspond to Count 1 are:

Zhang '285:	1-10, 15-16, 28-30, 33, 35-51
Imler '143:	56-57, 59, 61-65

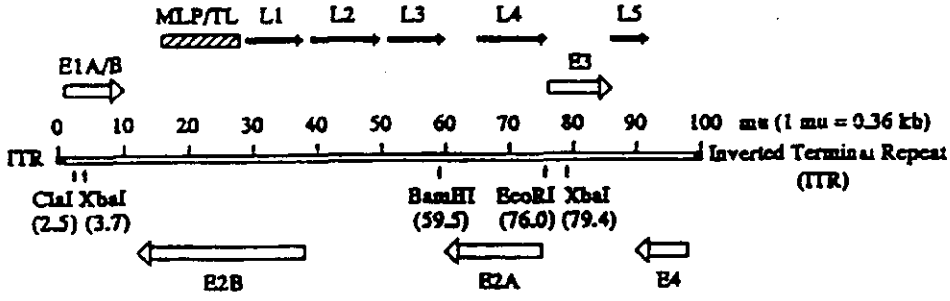
F16. The claims of the parties which do not correspond to Count 1, and therefore, are not involved in the interference, are:

Zhang '285:	17-23, 31-32, 34
Imler '143:	none

F17. Figure 1 in Zhang '285 (shown below) is said to describe

> the structure of the Ad5 genome. The genome is divided into 100 map units (mu). The open arrows represent early (E) transcription and the solid arrows represent late (L) transcription. The direction of transcription is indicated by arrows. Gaps in arrows indicate intervening sequences. The hatched box represents location of major late promoter and tripartite leader sequences (MLP/TL). The numbers in parenthesis indicate the map units. [Ex 1001, p. 17, ll. 24-31.]

[2] According to the Examiner, claims 38-48 of Zhang '285 are unpatentable.



F18. Zhang '285 describes

Adenoviruses ...[as] double-stranded DNA viruses with a linear genome of approximately 36 kb. A simplified map of the adenovirus type 5 (Ad5) genome with a few key landmarks is diagrammed in Figure 1. Both ends of the viral genome contain 100-200 base pair (bp) inverted terminal repeats (ITR), which are *cis* elements necessary for viral DNA replication and packaging. The early (E) and late (L) regions of the genome that contain different transcription units are divided by the onset of viral DNA replication. The E1 region (E1A and E1B) encodes proteins responsible for the regulation of transcription of the viral genome and a few cellular genes. The expression of the E2 region (E2A and E2B) results in the synthesis of the proteins for viral DNA replication. These proteins are involved in DNA replication, late gene expression, and host cell shut off (Renan, 1990). The products of the late genes, including the majority of the viral capsid proteins, are expressed only after significant processing of a single primary transcript issued by the late major late promoter (MLP). The MLP (located at 16.8 m.u.) is particularly efficient during the late phase of infection, and all the mRNAs issued from this promoter possess a 5' tripartite leader (TL) sequence which makes them preferred mRNAs for translation. [Ex 1001, p. 20, l. 28 - p. 21, l. 14.]

Other findings of fact follow below.

III. Imler preliminary motion 2

Nitz v. Ehrenreich, 537 F.2d 539, 543, 190 USPQ 413, 417 (CCPA 1976) stated that

> [t]he materiality of a limitation is directly related to its significance within the invention as a whole. Cf. In re Frilette, 58 CCPA 799, 436 F.2d 496, 168 USPQ 368 (1971). In McCabe v. Cramblet, supra, which we

quoted with favor in Brailsford v. Lavet, supra, this court stated:

> The first question for consideration is whether there is any patentable distinction between the counts here involved and said claims 1 to 5 of appellant's patent; or, in other words, do the claims of said patent and the counts of the interference call for the same invention? ... the test is whether the counts of the interference and the claims of the patent call for the same invention. ...

As set forth in 37 CFR § 1.601(n),

> [i]nvention "A" is the *same patentable* invention as an invention "B" when invention "A" is the same as (35 U.S.C. § 102) or is obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A." Invention "A" is a *separate patentable invention* with respect to invention "B" when invention A" is new (35 U.S.C. 102) and non-obvious (35 U.S.C. 103) in view of invention "B" assuming invention "B" is prior art with respect to invention "A".

Imler can establish that no interference-in-fact exists by showing that none of the involved Imler claims corresponding to the Count is anticipated or rendered obvious by any of the involved Zhang claims corresponding to the Count or vice versa. That is, no interference-in-fact is subject to a "one-way" test for patentable distinctiveness.

F19. All of the Zhang claims corresponding to the Count describe adenoviral (Ad) vectors wherein all of the E2 coding region has been deleted, i.e., the E2B gene region is missing as well as the E2A gene region.

F20. None of the involved Zhang claims encompass Ad vectors wherein only a part or all of the E2A gene is removed.

F21. All of the Imler claims corresponding to the Count describe recombinant adenoviruses wherein a part or all of the E2A gene region is missing.

F22. As noted by Imler, "none of Imler's claims require all of the E2 region to be deleted" (Paper 40, p. 2).

F23. By the same token, none of Imler's claims prohibit all of the E2 region to be deleted by virtue of the open claim language used, i.e., "comprising" and "having".

F24. Thus, none of Imler '143 claims 56-57, 59 and 61-65 anticipate any of Zhang '285 claims 1-10, 15-16, 28-30, 33 and 35-51.

F25. Dr. Monika Lusky-Helm testified for party Imler that

> In order to delete all of the E2 coding region, portions of the major late promoter and tripartite leader sequences, as well as coding regions of the L1 gene, which overlap E2B on the opposite DNA strand to the E2 sequences, must also be deleted (Ex 1002, ¶ 8).
>
> * * * * * *
>
> The precisely timed expression of the late region genes directed by the major late promoter and tripartite leader sequences is essential for the propagation of infectious viral particles (Ex 1002, ¶ 13).
>
> The requirement of deletion of the entire E2 coding region is a significant difference from requiring deletion of only part or all of the E2A region. The requirement of deletion of the entire E2 region in the Zhang claims necessarily requires deletion of the entire E2B coding region. [Ex 1002, ¶ 14.]
>
> * * * * * *
>
> In contrast to the E2B coding region, it is possible to delete part, or even all of the E2A gene coding sequence without touching a coding portion of any other gene (Ex 1002, ¶ 16).
>
> In view of the complexity of the E2B region, even if one skilled in the art knew that part or all of the E2A region could be deleted, they would not have had a reasonable expectation of success in using a vector in which the entire E2 coding region was deleted at the time the Zang [sic] application was filed (Ex 1002, ¶ 17).

F26. Zhang '285 asserts that

> [b]efore the present invention, complementation of the E2 regions of the adenoviral genome was not thought to be possible because of their size and complexity. For example, the E2A region which comprises about 6 kb, also comprises the L4 region in the reverse orientation. The E2B region, which is the largest of the early gene regions comprising about 10 kb, also comprises the major later promoter/tripartite leader region as well as the L1 gene in the reverse orientation. The tripartite leader region is a

> complex region of untranslated DNA that directs the cutting and splicing of the viral mRNA to direct the entire late life cycle of the virus. ... [Ex 1001, p. 8, l. 26 - p. 9, l. 3.]
>
> * * * * * *
>
> ...[O]wing to the genetic complexity and sheer size of the E2 region, it was believed that E2 region functions could not be successfully complemented by a helper cell host producer of those functions (Ex 1001, p. 23, ll. 12-15).

F27. Moreover, a 1997 publication by Amalfitano[3] suggested that only portions of the E2B gene region may be deleted. To wit,

> [w]e have investigated a different region of the viral genome, E2-b, which encodes the viral replication proteins which are absolutely required for Ad genome replication. ... [T]he deletion of the polymerase and preterminal protein genes will not be straightforward, since other viral regulatory elements are also present in this area, including the second and third tripartite leader sequences, the i-leader, portions of the major-late promoter intronic sequences (required for high-level transcription from the major-late promoter (MLP)), and the IVa2 gene. Despite this complexity, we anticipate that deletions of subportions of the polymerase and preterminal protein genes can theoretically approach at least 4.6 kb. [Ex 1003, p. 261, last ¶.]

We find the testimony of Dr. Lusky-Helm to be highly credible and consistent with assertions in Zhang '285 and the disclosure of Amalfitano, a reference published after the 1994 filing date of Zhang '285, i.e., deleting the E2B region results in deletion of gene regions essential for the propagation of infectious viral particles, e.g., MPL and TL gene regions. Therefore, based on the above, Imler '143 claims 56-57, 59 and 61-65 would not have rendered Zhang '285 claims 1-10, 15-16, 28-30, 33, 35-51 obvious because the Imler claims do not suggest deleting the entire E2B gene region in addition to the E2A gene region.

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[3] Amalfitano et al., "Isolation and characterization of packaging cell lines that coexpress the adenovirus E1, DNA polymerase, and preterminal proteins: implications for gene therapy," Gene Therapy, Vol. 4, pp. 258-263 (1997) (Ex 1003).

For the above reasons, Imler preliminary motion 2 is **granted**.

IV. Zhang preliminary motions 1 and 2

F28. "Original" claim 1 in Zhang '696 recites "[a]n adenovirus vector construct wherein all or part of the E2 region has been deleted from the adenovirus genome and heterologous DNA is inserted in its place, and wherein said adenovirus vector construct replicates in a helper cell." Zhang '696 claims 2-10 depend from claim 1. "Original" claim 11 in Zhang '696 recites "An adenovirus vector construct comprising, at least about 200 base pairs of the left ITR region of the adenovirus genome, more than 7.5 kb of heterologous DNA and at least about 200 base pairs of the right ITR region of the adenovirus genome." Zhang '696 claims 12-14 depend from claim 11. "Original" claim 15 in Zhang '696 recites "An adenovirus vector construct consisting essentially of map units 0-1.25 of the adenovirus 5 genome, at least 7.5 kb of heterologous DNA and map units 84.5 - 100 of the adenovirus 5 genome." [Ex 2001, pp. 45-46.]

F29. Claim 1 of U.S. Patent 5,882,877 issued March 16, 1999 to Gregory et al. (Gregory '877) (Ex 2500, copy attached) reads:

> An adenoviral vector comprising an adenovirus genome from which the E1, E2, E3 and E4 regions and late genes of the adenovirus genome have been deleted and additionally comprising a nucleic acid of interest operably linked to expression control sequences.

F30. Gregory '877 issued from U.S. application 08/895,194, filed July 16, 1997, which is a continuation of U.S. application 08/136,742, filed October 13, 1993 (now U.S. Patent 5,670,488), which is a continuation-in-part of U.S. application 07/985,478, filed December 3, 1992 (Ex 2500, front page).

F31. Gregory '877 is prior art to Zhang '696 at least as of October 13, 1993.[4]

F32. The "new" claims Zhang proposes to add to its continuation application Zhang '696 recite "[a]n adenovirus vector construct wherein at least part of the E2 coding region has been deleted from the adenovirus genome ... wherein the deletion causes said adenovirus vector to be replication defective" (new claim 28), "...wherein the at least part of the E2 coding region comprises at least part of the E2A coding region" (new claim 29), and "[t]he adenovirus vector as in any one of claims 28, 29 and 30, further comprising a deletion in a second early gene region" (new claim 31). Also, new claims 31-41 and 43-48 recite adenovirus vector constructs wherein the E2A region is deleted alone or in combination with the E1, E3 and/or E4 regions. [Ex 2001, "PRELIMINARY AMENDMENT".]

F33. In its reply, Imler urges us to decline from deciding Zhang preliminary motions 1 and 2 (Paper 44, p. 4) and indicates that it "intends to challenge Zhang's assertions of patentability" (id., p. 2).

Dismissing Zhang preliminary motions 1 and 2 would not only allow the Examiner to assess Zhang's newly proposed claims in Zhang '696 for compliance with 35 U.S.C. § 112, first paragraph, but also allow the Examiner to consider whether one or more of the pending claims in Zhang '696 is anticipated or rendered obvious by Gregory '877. In addition, as both Zhang and Imler are applicants, dismissing Zhang preliminary motions 1 and 2 would extending the patent term protection of the claims of Imler and

[4] We suggest that the Examiner also determine whether Gregory '877 is prior art to Imler '143 and take whatever action, if any, is appropriate.

Zhang on the basis of the interference. Furthermore, party Zhang would not be estopped from seeking a second interference involving "[a]n adenovirus vector construct wherein at least part of the E2 coding region has been deleted from the adenovirus genome ... wherein the deletion causes said adenovirus vector to be replication defective" (new claim 28). Moreover, party Imler requests us to dismiss Zhang preliminary motions 1 and 2 (Paper 44, p. 4).

For the above reasons, Zhang preliminary motions 1 and 2 are **dismissed** without prejudice to further proceedings before the primary Examiner. Should the primary Examiner determine that both Imler and the newly filed continuing Zhang application '696 contain allowable claims to an Ad vector wherein at least part of the E2 coding region has been deleted and packaging cell lines therefore, a second interference may be appropriate. 37 CFR § 1.604.

V. Recommendation under 37 CFR § 1.659(c)

We recommend that upon resumption of ex parte prosecution of Imler '823, the Examiner consider whether Imler '143 claims 56-57, 59 and 61-65 satisfy the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. As noted above, Imler claims 56-57, 59 and 61-65 encompass recombinant adenoviruses wherein the entire E2 region is removed. The Examiner should consider in particular whether Imler '143 describes and enables Ad vectors wherein the E2B region is removed and whether Imler '143 provides a complementing cell line to replace Ad functions deleted by removal of the E2B region, e.g., functions of the MLP and TL gene regions.

VI. Order

Therefore, upon consideration of the record and for the reasons given, it is

ORDERED that Imler preliminary motion 2 is **granted**.

FURTHER ORDERED that there is no interference-in-fact between Imler '143 claims 56-57, 59 and 61-65 and Zhang '285 claims 1-10, 15-16, 28-30, 33 and 35-51.[5]

FURTHER ORDERED that a final judgment is entered that there is no interference-in-fact, between (1) Imler '143 claims 56-57, 59 and 61-65 and (2) Zhang '285 claims 1-10, 15-16, 28-30, 33 and 35-51.

FURTHER ORDERED that the subject matter of Imler '143 claims 56-57, 59 and 61-65 is no impediment under the law to the issuance of a patent to Zhang '285.

FURTHER ORDERED that the subject matter of Zhang '285 claims 1-10, 15-16, 28-30, 33 and 35-51 is no impediment under the law to the issuance of a patent to Imler '143.

FURTHER ORDERED that Zhang preliminary motions 1 and 2 are **dismissed**, without prejudice to further proceedings before the primary Examiner.

FURTHER ORDERED that if there is a settlement agreement between the parties, attention is directed to 35 U.S.C. § 135(c).

FURTHER ORDERED that attention is directed to 37 CFR § 1.661.

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[5] According to the Examiner, Zhang '285 claims 35-48 are unpatentable.

FURTHER ORDERED that a copy of this paper shall be made of record in files of applications 08/222,285 and 09/218,143.

RICHARD TORCZON
Administrative Patent Judge

CAROL A. SPIEGEL
Administrative Patent Judge

MICHAEL P. TIERNEY
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

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